REMARKS

In the Office Action dated January 29, 2003, claims 7-18 are pending. Claims 7, 9-13 and 17-18 are withdrawn from consideration. Claims 8 and 14-16 are under examination.

Claims 8 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as allegedly not supported by an enabling disclosure.

It is observed that claims 8 and 14-16 are directed to methods of regeneration of bone or cartilage by administration of a DNA molecule. The DNA molecule is characterized as comprising a nucleotide sequence selected from SEQ ID NO: 20, a nucleotide sequence having at least about 79% identity as SEQ ID NO: 20 and coding for a SOX-9 polypeptide, or a nucleotide sequence which hybridizes to SEQ ID NO: 20 under standard hybridization conditions and encodes a SOX-9 polypeptide.

The Examiner recognizes that the present specification teaches that the human Sox-9 gene (SEQ ID NO: 20) plays an important role in development (page 5), and that experimental bone fracture induces the expression of the SOX-9 polypeptide. However, the Examiner contends that the specification does not demonstrate any therapeutic effect of a Sox-9 gene in any animal having a bone or cartilage disease. The Examiner is of the opinion that there is no reasonable correlation between the expression of endogenous Sox-9 during embryogenesis and a therapeutic effect in a treatment of any bone or cartilage associate disorder in any animal. Moreover, the Examiner alleges that the specification provides no *in vivo* or *in vitro* examples to demonstrate the biological activity of any DNA sequence recited in the claims for regeneration of bone or cartilage.

Applicants respectfully submit that the expression of Sox-9 genes is thoroughly characterized in the specification. Specifically, the specification discloses that the expression of the murine Sox-9 gene preceded the deposition of cartilage in all skeletal elements and ceased soon after deposition of cartilage. See pages 20-22 of the specification. In addition, the specification discloses that Sox-9 expression was transiently induced by bone fracture.

Applicants respectfully submit that the characterizations of the Sox-9 genes, as provided in the specification, are reasonably related to the therapeutic methods using a Sox-9 nucleic acid, as instantly claimed. For example, administration of a Sox-9 nucleic acid molecule could supply the requisite production of the Sox-9 protein in a subject suffering a bone disorder wherein the expression of Sox-9 is insufficient or the SOX-9 proteins expressed are inactive.

Applicants provide herewith several references (Exhibits 1-6) as further support of the biological activity and therapeutic effects of Sox-9 genes. Specifically, Bi et al. (*Nature Genetics* 22: 85-89,1999, **Exhibit 1**) and Healy et al. (*Developmental Dynamics*, 215: 69-78, 1999, **Exhibit 2**) both identify Sox-9 as a transcription factor that is essential for chondrocyte differentiation and cartilage formation. Rabie et al. (*American Journal of Orthodontics and Dentogacial Orthopedic*s, 122(4): 401-409, 2002, **Exhibit 3**) disclose that the expression of Sox-9 in chondrocytes regulates the synthesis of type II collagen and subsequently affects condylar cartilage formation. Sakano et al. (*Journal of Bone and Mineral Research* 14: 1891-1901,1999, **Exhibit 4**) report certain observations that suggest that cell differentiation during fracture healing is controlled by specific transcriptional factors, such as Sox-9, which regulate phenotypic changes of the cells. Bell et al. (*Nature Genetics*, 16: 174-178,1997, **Exhibit 5**) demonstrate that *COL2A1* expression is directly regulated by SOX9 protein *in vivo*.

Applicants direct the Examiner's attention especially to Tsuchiya et al. (*Biochemical and Biophysical Research Communications*, 301: 338-343, 2003, **Exhibit 6**). Tsuchiya et al. investigated chondrogenesis of cell-mediated S*ox9* gene therapy as a new treatment regimen for cartilage regeneration. pIRES2-EGFP vector containing a full-length mouse *Sox9* cDNA was transfected into bone marrow-derived mesenchymal stem cells (MSCs) and chondrogenic differentiation of these cells was evaluated. *In vitro* high density micromass culture of these *Sox9* transfected MSCs demonstrated that a matrix-rich micromass aggregate with EGFP expressing MSCs was positively stained by Alcian blue and type II collagen. The *Sox9* transfected MSCs were then loaded into the diffusion chamber and transplanted into

athymic mice to analyze *in vivo* chondrogenesis. A massive tissue formation in about 2mm diameter was visible in the chamber after 4 weeks transplantation. Histological examinations demonstrated that both Alcian blue and type II collagen were positively stained in the extracellular matrix of the mass while type X collagen was not stained. These results support the understanding that cell-mediated *Sox9* gene therapy can be applied to treat hyaline cartilage damage.

Applicants respectfully submit that the above references provide evidence of what is asserted and claimed in the present application – namely, Sox-9 nucleic acid molecules function as transcriptional factors to regulate expression of proteins essentially for bone or cartilage formation, and are beneficial for use in regeneration of bone or cartilage. Although the above references were published after the filing date of the present application, Applicants observe that the results described in these references were achieved using techniques that were routine to those skilled in the art at the time the present application was filed. In this regard, Applicants submit that post-filing publications can be offered as evidence of the level of skill in the art at the time the application was filed. See Gould v. Quigg, 822 F.2d 1074, 3 USPQ2d 1302 (Fed. Cir. 1987).

The Examiner also alleges that neither the specification nor the claims delineate the subjects or the type of bone diseases being treated, the target sites, the effective dosage for accomplishing a therapeutic effect *in vivo*, the routes of administration, or the effect of the claimed methods.

Applicants respectfully submit that the specification has clearly provided that the therapeutic methods of the present invention can be applied to animal subjects including humans, livestock, domestic animals and other animal species. See, e.g., page 10, lines 5-15. The specification also provides that the claimed therapeutic methods are beneficial to ameliorate conditions of cartilage or bone breakage, degeneration, depletion or damage, which may be caused by aging, genetic or infectious disease, wear and tear, physical stress, accident,

or other cause. See page 10, lines 1-5, for example. Applicants have amended independent claim 8 to delineate the subject being treated as "an animal subject suffering breakage, degeneration, depletion or damage of bone or cartilage", consistent with the instant disclosure. No new matter is introduced by such amendment.

In addition, Applicants respectfully submit that the specification describes suitable routes of administration. Specifically, the administration can be achieved by injection, implantation, instillation or other means of a Sox-9 nucleic acid molecule or by cells that have been modified *ex vivo*. See page 11, line 1 to page 12, line 8. Given the present teaching, and depending upon the condition of the subject and the manner of administration, those skilled in the art would be able to determine the effective dosage of the Sox-9 nucleic acid molecule for administration.

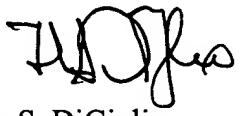
The Examiner also alleges that the specification does not enable a skilled artisan to determine without undue experimentation as to which of the DNA sequences having up 21% variation from SEQ ID NO: 20 exhibits a biological function as a "SOX-9" protein.

In an effort to favorably advance the prosecution of the present application, Applicants have amended the claims to define the DNA molecule as comprising "the nucleotide sequence as set forth in SEQ ID NO: 20 or a nucleotide sequence coding for a SOX-9 polypeptide wherein said SOX-9 polypeptide comprises the amino acid sequence as set forth in SEQ ID NO: 21". Applicants reserve the right to pursue the subject matter encompassed by the claims as originally filed, in a continuation application.

In view of the foregoing, it is respectfully submitted that the claimed methods of regeneration of bone or cartilage using a Sox-9 DNA molecule is fully supported by the specification. Those skilled in the art would be able to practice the claimed methods without undue experimentation. Thus, the rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Accordingly, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Encls.: Exhibits 1-6